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LTD, RP and motor learning

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Conflict of interest notification

There are no potential conflicts of interest in this manuscript.

Abstract

Long-term depression (LTD) at excitatory synapses between parallel fibers and a Purkinje cell has been regarded as a critical cellular mechanism for motor learning. However, it was demonstrated that normal motor learning occurs under LTD suppression, suggesting that cerebellar plasticity mechanisms other than LTD also contribute to motor learning. One candidate for such plasticity is rebound potentiation (RP), which is long-term potentiation at inhibitory synapses between a stellate cell and a Purkinje cell. Both LTD and RP are induced by the increase in postsynaptic Ca^{2+} concentration, and work to suppress the activity of a Purkinje cell. Thus, LTD and RP might work synergistically, and one might compensate defects of the other. RP induction is dependent on the interaction between $GABA_A$ receptor and $GABA_A$ receptor binding protein (GABARAP). Transgenic mice expressing a peptide which inhibits binding of GABARAP and $GABA_A$ receptor only in Purkinje cells, show defects in both RP and adaptation of vestibulo-ocular reflex (VOR), a motor learning paradigm. However, another example of motor learning, adaptation of optokinetic response (OKR) is normal in the transgenic mice. Both VOR and OKR are reflex eye movements suppressing the slip of visual image on the retina during head movement. Previously we reported that delphilin knockout mice show facilitated LTD induction and enhanced OKR adaptation,

but we recently found that VOR adaptation was not enhanced in the knockout mice. These results together suggest that animals might use LTD and RP differently depending on motor learning tasks.

LTD and RP

At excitatory glutamatergic synapses between parallel fibers and a Purkinje cell, long-term depression (LTD) of glutamate responsiveness is induced by coupled activation of parallel fibers and a climbing fiber, which has been regarded as a critical cellular mechanism for motor learning [1, 2]. However, this idea has been challenged by demonstration of normal motor learning under suppression of LTD [3, 4], which suggests that plasticity mechanisms other than LTD contribute to motor learning [2, 5, 6]. Indeed, many types of synaptic plasticity have been reported in the cerebellar cortex and nuclei at various synapses such as mossy fiber–granule cell, parallel fiber-Purkinje cell, parallel fiber-stellate cell, stellate cell-Purkinje cell synapses [2]. In addition, plasticity of dendritic excitability of a Purkinje cell was reported [7]. Among them one candidate plasticity mechanism which could compensate defects of LTD, is rebound potentiation (RP) at synapses between an inhibitory stellate cell and a Purkinje cell in the molecular layer. RP is long-term potentiation of GABA responsiveness of a Purkinje

cell induced by climbing fiber activation [8]. There are similarities between LTD and RP. One is that both are induced by climbing fiber activity or by the increase in intracellular Ca^{2+} concentration in a Purkinje cell [9, 10, 11], and the other is that both work to suppress the Purkinje cell activity. We actually found that LTD and RP were induced simultaneously by depolarizing conditioning stimulation of a rat cultured Purkinje cell, indicating that LTD and RP can be induced simultaneously in certain conditions. In addition, some intracellular signaling molecules such as mGluR1, cAMP, cGMP, CaMKII etc. are involved in both LTD and RP [12, 13]. Therefore, some LTD-deficient mutant mice such as mGluR1 knockout mice [14] might be also defective in RP, leading to a possibility that some mutant mice show motor learning failures because of defects in both LTD and RP. On the other hand, a mutant mouse in which probably only LTD is impaired might show apparently normal motor learning [4]. However, we would like to note that there is a difference in the induction condition between LTD and RP. Not only climbing fiber activity but also parallel fiber activity is necessary for LTD induction [1], whereas only climbing fiber activity is sufficient for RP induction [8]. Thus, LTD induction is homosynaptically regulated and synapse specific, whereas RP is heterosynaptically induced and can be a cell-wide phenomenon, although there is a synapse-specific regulation mechanism for RP [15].

RP-deficient mice

Molecular regulation mechanisms of RP induction has been studied extensively [13], and it was revealed that interaction of $GABA_A$ receptor binding protein (GABARAP) and $GABA_A$ receptor is necessary for RP induction [16]. This result prompted us to examine physiological roles of RP using RP-deficient mice. To this end, we generated transgenic mice, in which a peptide blocking interaction of GABARAP and $GABA_A$ receptor was expressed only in Purkinje cells [17]. The transgenic mice fail to show RP as expected, and have defects in adaptation of vestibulo-ocular reflex (VOR), a well-known motor learning paradigm. However, they show normal adaptation of optokinetic response (OKR), another example of motor learning. Both VOR and OKR are reflexes to stabilize the visual image on the retina during head motion. In VOR vestibular organs such as semi-circular canals detect head rotation, and drive eye balls to turn in the opposite direction of head turn reducing the blur of visual image. The timing and amplitude of VOR need to be precisely regulated so that it works adequately in daily life. Adaptation of VOR occurs when the eyeball motion fails to stabilize the visual image on the retina. For example, if rotation of a head-fixed animal is coupled with rotation of surroundings in the opposite direction or in the same direction, the gain

of VOR increases or decreases respectively. These are gain-up and gain-down adaptation of VOR, and both are defective in RP-deficient transgenic mice. In OKR, the visual information about the relative movement of animal's surrounding drives the eyeball movement so that the latter follows the former. Often eyeball movement is too slow to follow the surrounding's movement at first. However, if movement of the visual field continues, the eye ball movement gets faster to better catch up the movement of visual field. This is adaptation of OKR, which is not affected in the RP-deficient transgenic mice. These results suggest that RP is involved in a certain type of motor learning, and that contribution of RP to motor learning might be different among tasks.

Mutant mice with facilitated LTD induction

GluD2 is an ionotropic glutamate receptor-related molecule selectively expressed in Purkinje cells and necessary for LTD induction [18, 19], and delphilin is a GluD2 binding protein which is also specifically expressed in Purkinje cells. It was previously reported that in delphilin knockout mice LTD is more easily induced than in wild-type mice and OKR adaptation is enhanced [20]. LTD is induced by a small number of conditioning depolarization coupled with parallel fiber stimulations or in the presence of a Ca^{2+} chelator EGTA in a delphilin knockout Purkinje cell. In these conditions a

wild-type Purkinje cell fails to show LTD. In addition, the speed of gain increase in OKR adaptation is larger in delphilin knockout mice than in wild-type mice, suggesting that facilitation of LTD induction might contribute to enhancement of motor learning. However, we recently found that VOR adaptation was not enhanced in delphilin knockout mice compared with wild-type mice. These results together suggest that facilitated LTD might enhance OKR adaptation but not VOR adaptation. Thus, contribution of LTD to motor learning might be different among tasks as that of RP.

In summary, LTD and RP can be induced simultaneously in certain conditions, and contribution of LTD or RP to motor learning seems to be different among tasks. Thus, not only LTD but also other plastic mechanisms including RP contribute to motor learning, and that the contribution of each cerebellar plastic mechanism to motor learning is likely to be different among tasks and in various conditions.

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